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Clinical Proceedings

OF THE CHILDREN'S HOSPITAL

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(1) Jeans, P. C., in A. M. A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, pp. 275-278.

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PEDIATRIC RADIOTHERAPY

Isidore Lattman, M.D.*

A fallacious belief that cancer is a disease particularly of middle and old age is prevalent among non-physicians and some physicians. Neoplasms may occur in any age group and the pediatrician is well acquainted with this group of diseases. However, malignant disease in children is not common. Approximately 0.8 per cent of the total admissions to Children's Hospitals in Great Britain and the United States are caused by some form of malignancy. This statistic probably is not accurate because many children with malignant tumors of the eye and central nervous system are admitted directly to specialized tumor hospitals. In addition, the leukemias and Hodgkin's disease have been classified as malignant lesions only as recently as the past decade.

The establishment of cancer clinics and tumor boards in the United States has resulted in a more cancer-conscious medical profession. The advances in antibiotics, chemotherapy, fluid and electrolyte therapy and pediatric surgery, all associated with increased survival, have resulted in a relative increase in the mortality rate caused by cancer in children so that it has now become one of the most serious common problems in pediatrics. In the February 1951 issue of the *Clinical Proceedings of the Children's Hospital*, Dr. E. Clarence Rice states, "When one considers that cancer in children, leukemia included, causes more deaths than either measles, scarlet fever, epidemic meningitis, poliomyelitis or diabetes mellitus, it will be apparent that we are confronted with a serious problem."

TYPES OF TUMORS

As in the adult, a variety of malignant lesions may occur in infancy and childhood although some are more common than others. No organ may be considered immune. In children, the lymphatic system is most commonly involved. This is followed by embryonal tumors, neurogenic tumors, and bone tumors. Other tumors are rare types.

1. *The lymphatic system:* This group of malignant diseases includes the leukemias, the lymphoblastomas, and Hodgkin's disease. Lymphoblastomas may occur anywhere in the body. We recently had a histologically proven case of lymphosarcoma of the small intestine. Occasionally, a patient with lymphosarcoma may develop leukemic changes in his blood stream, a condition called leukosarcoma. At the present time, these diseases are fatal. In the past 8 to 10 years important strides have prolonged the life and

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made the patient more comfortable during the duration of illness. Drugs such as the folic acid antagonists, adrenocorticotropic hormones and cortisone are effective but only palliatively. Blood transfusions remain a common symptomatic measure. Radiation therapy is an important adjunct when it becomes necessary to relieve pressure symptoms caused by hepatosplenomegaly or enlarged mediastinal lymph nodes.

2. *Embryonal types of tumors:* These include the Wilms' tumor and malignant teratomas. There are now reported some 20 year cures of Wilms' tumors treated by a combination of surgery and radiation. We have three 8 year cures at our hospital.

3. *The neurogenic tumors:* These include the neuroblastomas and malignant lesions arising in the central nervous system such as the astrocytomas, astroblastomas, medulloblastomas, glioblastomas, and retinoblastomas. The neuroblastoma usually arises in the adrenal cortex but may arise anywhere in the sympathetic nervous system (sympathicoblastoma). These tumors occasionally change from malignant neurocytomas or neuroblastomas to benign ganglioneuromas. Such an instance was reported in 1927 by Cushing and Wolback and by numerous investigators since then. This rare phenomenon has been noted to take place with or without treatment.

4. *Bone tumors:* The more common types of these malignant growths occurring in children include osteogenic sarcoma and Ewing's tumor (endothelioma of bone).

5. *Rare tumors:* In addition, less frequent forms of cancers may be found in children, such as adenocarcinomas of the kidney and thyroid gland.

If the problem of cancer in childhood is to be helped, then the entire medical arsenal at our command must be brought into action. Optimal results can be achieved only by a cooperative effort on the parts of the various medical departments and surgical specialties. This includes the pediatrician, the surgeon, the pathologist, and the radiologist. All play important responsible parts in the management and treatment of the infancy and childhood malignancies.

RADIOTHERAPY

In general the sensitivity of tumor cells to irradiation depends on many factors and these must be known before treatment is instituted.

(1) The *histiogenesis of the tumor cells* must be ascertained because different cells respond differently. As a rule lymphatic cells are the most radiosensitive and neurogenic cells and bone cells the most resistant. A. U. Desjardin has shown the difference in radiosensitivity of the different cells of the body and has listed them as follows, in order of their sensitivity (*Science* 75, 569, 1932):

Lymphoid cells (lymphocytes);
Polymorphonuclear and eosinophilic leukocytes;
Epithelial cells

a. Basal epithelium of certain secretory glands, especially salivary glands.
b. Basal epithelium (spermatgonium) of testis and follicular epithelium of the ovary.
c. Basal epithelium of the skin, mucous membrane, and certain organs such as stomach and small intestine.
d. Alveolar epithelium of the lungs, bile ducts (liver).
e. Epithelium of the tubules of the kidneys.

Endothelial cells of blood vessels, pleura and peritoneum.
Connective tissue; muscle; bone and nerve cells.

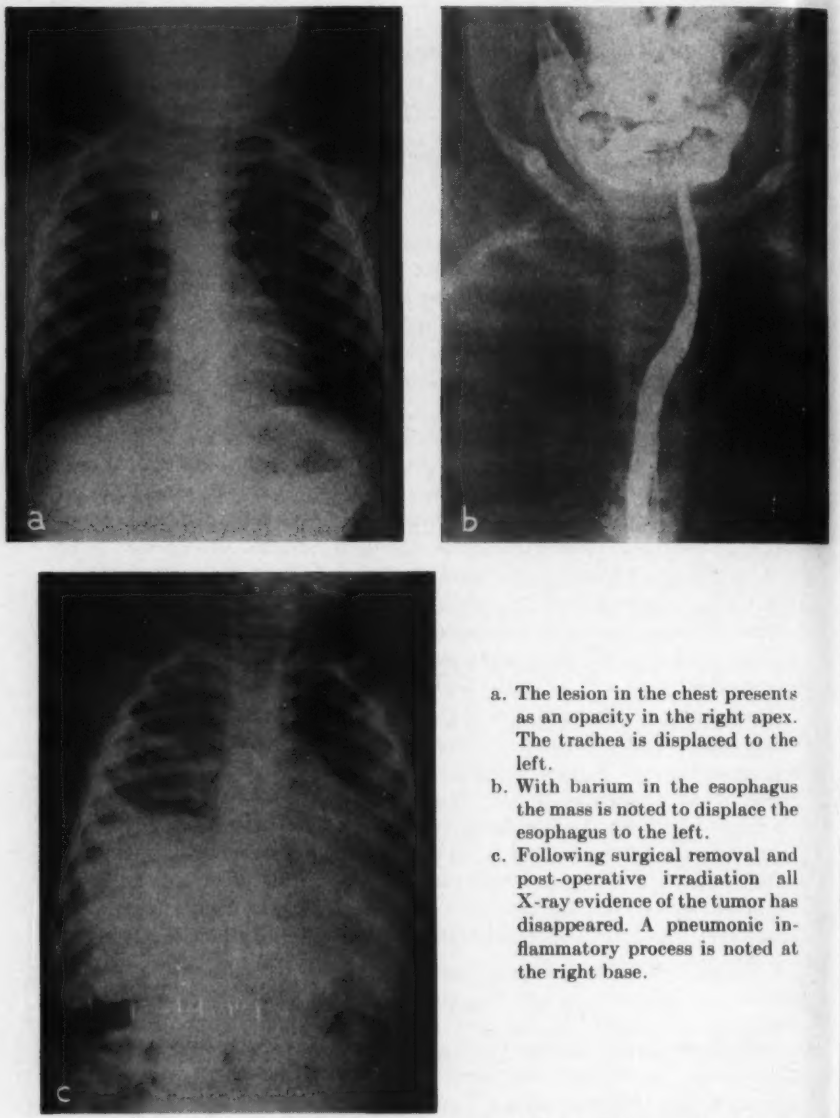
The high radiosensitivity of lymphoid cells were demonstrated by Heinecke as early as 1903.

(2) The *degree of differentiation* of the malignant cells should be determined. The Law of Bergonie and Tribandeau states that embryonal cells, dividing cells, and hyperchromatic cells are more sensitive to radiation. (3) In general the sensitiveness of tumor cells to x-rays is more or less proportional to the *rate of metabolism* of the cell. (4) In addition, many *other factors* are important. These include inflammation, infection, the kind of stroma the tumor is surrounded by, the location of the tumor, its vascularity, whether it was previously irradiated, the general physical condition of the patient, and even the personal factor. As a rule infants and children tolerate irradiation as well as adults and as they do surgery.

In general, it can be stated that surgery is the treatment of choice in those cancers which can be removed in their entirety such as the malignant lesions of bone, cartilage, muscle, fibrous and fatty tissue, and some of the tumors of nerve tissue. Radiotherapy is the treatment of choice in tumors of the lymphatic system. A combination of both forms of treatment must be employed in the embryonal tumors and whenever the entire tumor cannot be removed surgically, particularly in cancers of the brain and spinal cord. Neoplasms of the skin or mucous membranes, which occur only rarely in childhood, can be treated by contact therapy with considerable success.

METASTASES

One of the characteristics of malignant disease in childhood is that metastases usually occur early and rapidly. For this reason early diagnosis and intensive therapy are essential. These metastatic lesions may appear anywhere in the body. As a rule metastases to the lungs are as radiosensitive as the tumors from which they originate. The site of a metastatic lesion



a. The lesion in the chest presents as an opacity in the right apex. The trachea is displaced to the left.
b. With barium in the esophagus the mass is noted to displace the esophagus to the left.
c. Following surgical removal and post-operative irradiation all X-ray evidence of the tumor has disappeared. A pneumonic inflammatory process is noted at the right base.

FIG. 1. Chest X-rays of an 18 month old colored male with a microscopic diagnosis of an embryonal neurogenic-type of tumor of the right chest.

a. Chest X-ray six months following surgery. A metastatic lesion is seen in the periphery of the left lung in the third interspace anteriorly.
b. 11 days after radiotherapy the metastatic lesion is noted to be dissolving.
c. One year later the chest is normal. 8 years after operation this patient is well and asymptomatic.

FIG. 2. Chest X-rays of a five year old white female with a microscopic diagnosis of Wilms' tumor of the right kidney which was removed surgically.

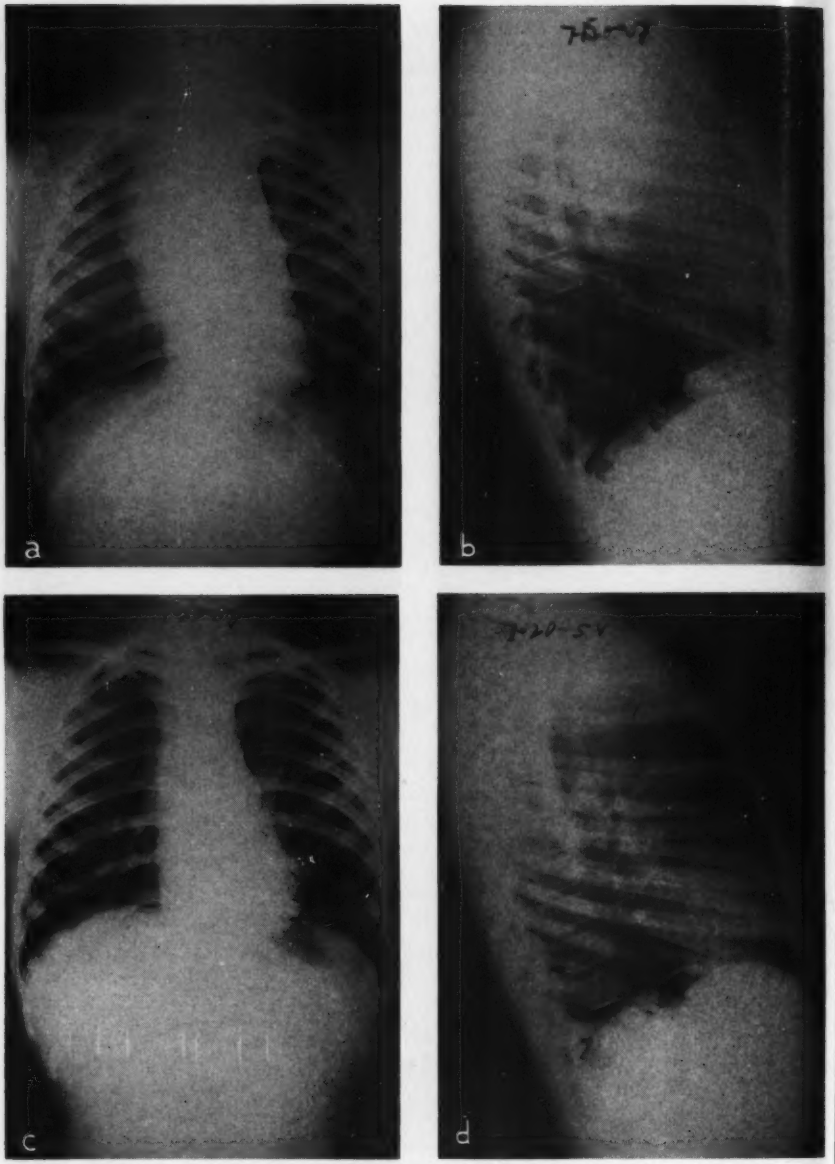


FIG. 3. Chest X-rays of an 11 year old white male with a diagnosis of lymphosarcoma confirmed by lymph node biopsy.

a. and b. AP and lateral views of the chest demonstrate a supracardiac, anterior mediastinal mass.

c. and d. AP and lateral views of the chest five days following radiotherapy. A total of 250r was given. All evidences of the lesion have disappeared. This patient presented with symptoms of a superior vena cava syndrome. The clinical response was as dramatic as the radiological even though temporary.

FIG. 4. AP and lateral views of the bones of the right upper extremity in a three year old oriental male with a confirmed diagnosis of bone metastasis from a Wilms' tumor four months after surgery.

a. The metastasis is seen in the lower portion of the right humerus. There is periosteal elevation, and destruction of the cortex, medulla, and metaphysis.

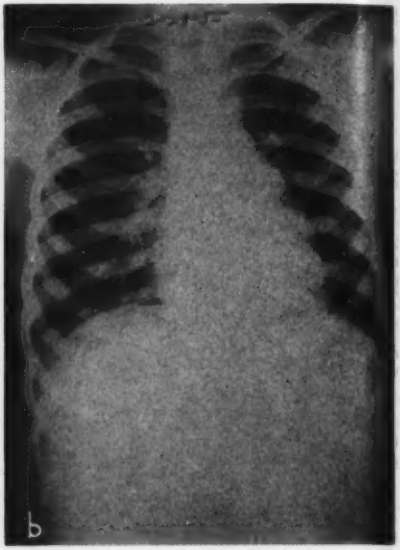
b. Two months following radiotherapy X-rays demonstrate almost complete disappearance of these changes.

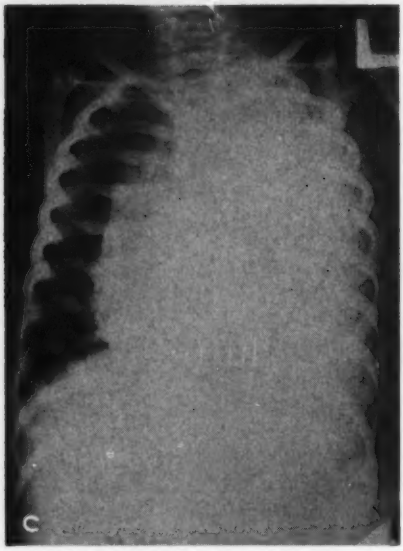
should not cause radiotherapy to be deferred. For example, metastasis to the lungs or bones should be treated.

When the choice to irradiate a malignant neoplasm is made, a plan of therapy must be mapped out, whether it be a plan to effect a cure or to palliate and prolong life. The ideal naturally is to cure. However, this is not very often possible in cancer therapy, especially in infants and children.

EFFECT ON OTHER TISSUES

Radiotherapy to deep seated cancers must pass through the skin and intervening structures before it reaches the malignant growth. Therefore the radiologist must be aware of the biologic effects of irradiation on normal tissues as well as its effects on epiphyseal growth and upon the generative organs. A good general rule to follow is to treat as small an area as possible. Unfortunately, it is impossible to deliver a lethal dose of x-rays to a deep





a. The lesion is visualized on X-ray as an opacity which almost completely fills the left chest. The trachea, mediastinum and the heart are displaced to the right.
b. One month after radiotherapy the X-ray of the chest is normal.
c. One month later massive recurrence of the lymphoblastoma is noted.

FIG. 5. Chest X-rays of a five year old white female with a confirmed microscopic diagnosis of lymphoblastoma.

seated tumor without damaging the surface and intervening tissue. Therefore, the next best course is to attempt to deliver a biologically effective dose to the malignant lesion with as little injury as possible to the normal intervening tissues. This depends to a great extent upon the experience and competence of the radiologist. Great care must be exercised in the treatment of the extremely radiosensitive tumors such as the lymphoblastomas especially when they are located in the chest, mediastinum, or gastrointestinal tract. The death of cells may occur so rapidly as to cause rapid local tissue damage, absorption and toxicity, and occasionally even obstruction of the respiratory passages.

Radiotherapy is also used effectively in numerous other lesions in infancy and childhood. A few of the more common of these include hemangiomas, hyperplasia of lymphatic and thymic tissue, non-specific and tuberculous cervical adenitis, some stages of the reticuloendothelioses, and many skin diseases and keloids. In the past 20 years we have epilated by radiation several thousand cases of ringworm of the scalp. In fact, radiation is by far the treatment of choice for this common infection.

In conclusion, the pediatric radiologist is not only helpful in diagnosis of the diseases of infancy and childhood, but often is equally helpful in the treatment of these illnesses. Together with the other medical specialists he plays an important part in managing the problem of infancy and childhood cancer. The accompanying radiographs and captions are examples of the effectiveness of radiotherapy in childhood tumors.

THE ETIOLOGY, DIAGNOSIS AND TREATMENT OF HYPOGLYCEMIA

Enid F. Gilbert, M.D.

INTRODUCTION

Considerable advances in the treatment of the syndrome of hypoglycemia have been made, particularly in the treatment of idiopathic spontaneous hypoglycemia of infancy. Therefore it is important that the clinician understand it fully.

Simply stated, hypoglycemia is an abnormally low blood glucose level. In infants and children, as well as in adults, the blood sugar level at which hypoglycemia symptoms may occur is 40 mg./100 ml.*

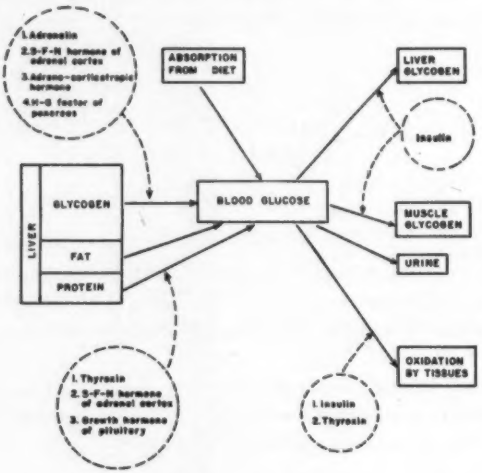
* This value is based on the Folin-Wu method of blood sugar determination in which 70 mg./100 ml. is considered normal. Central nervous system symptoms however do not usually appear until the level is 40 mg./100 ml. Using other procedures for the determination of "blood sugar" these values require adjustment.

The symptoms and signs of hypoglycemia are actually dependent, in large measure, on the glucose level of the cerebro-spinal fluid. Therefore it should be mentioned that the level of this carbohydrate in the spinal fluid generally parallels that of the blood sugar. However, the quantitative value of the former lags behind that of the latter. This is demonstrated by the fact that the normal blood sugar–spinal fluid ratio of 2:1 may be diminished or even reversed with the rapid onset of hypoglycemia.

NORMAL MECHANISMS CONTROLLING BLOOD SUGAR

Currently accepted mechanisms of blood sugar control in the normal individual are presented in Figure 1. The sources contributing to the blood glucose are absorption from the diet, glycogen-glucose conversion in the liver, which is increased by adrenalin and reversed by insulin, glyconeogenesis from protein, and gluconeogenesis from fat. Mechanisms which lower the blood sugar include oxidation by tissues, conversion to muscle and liver glycogen, and loss in the urine.

Chemoreceptors in the adrenal medulla are sensitive to variations in the level of blood sugar. Hyperglycemia initiates parasympathetic action which stimulates the islet cells of the pancreas. The islet cells are also directly sensitive to hyperglycemia inasmuch as increased insulin secretion occurs in response to hyperglycemia in the denervated pancreas.



PHYSIOLOGICAL FACTORS REGULATING BLOOD GLUCOSE CONCENTRATION

FIG. 1

Hypoglycemia conversely initiates sympathetic action stimulating the adrenal medulla to produce adrenalin. Adrenalin is the principal mechanism for increasing glycogenolysis in the liver. In addition adrenalin depresses utilization of glucose in the tissues by acting directly on the anterior pituitary and indirectly through the action of adrenocorticotropic hormone. The SFN hormone (Sugar-Fat-Nitrogen hormone) of the adrenal cortex also serves to increase protein-glucose conversion in the liver through the process of gluconeogenesis. The mechanism of the action of the several hormones is probably via their action on the enzymes carrying out the reactions indicated in Fig. 1.

SYMPTOMS AND SIGNS OF HYPOGLYCEMIA

Hypoglycemia is characterized by symptoms referable to the central nervous system, such as fatigue, weakness, flushing, sweating, speech and visual disturbances, incoordination, tremor, syncope, convulsions, and coma. The above are arranged in approximate relation to the increasing severity of the hypoglycemia. Interference with the function of the brain probably begins in the cerebral cortex and gradually progresses to the more primitive centers and ultimately to the medulla. In children the manifestations may be confined to irritability, and behavior changes if the hypoglycemia is relatively mild. Vomiting is fairly frequent in children but uncommon in adults, in whom hunger is a more frequent manifestation. The body temperature is likely to be lowered. There may be tachycardia and extrasystoles, which have been attributed to sympathetic stimulation in an effort to correct the hypoglycemia. The tremor, flushing, sweating, and coldness are probably due to concomitant release of adrenalin.

ETIOLOGY OF HYPOGLYCEMIA

A simple classification based on etiology is as follows:

A. Hyperinsulinism, relative
   1. Decreased glucose absorption from the gastro-intestinal tract
      (a) Starvation, vomiting, etc.
      (b) Celiac disease
   2. Decreased glycogen-glucose conversion
      (a) Liver disease
      (b) Glycogen storage disease (von Gierke's disease)
      (c) Galactosemia
   3. Defective renal tubular reabsorption
      (a) Renal glycosuria
      (b) de Toni-Fanconi syndrome
      (c) Lead poisoning
      (d) Phlorizin and dinitrophenol poisoning

4. Endocrine factors
   (a) Adrenocortical hypofunction,—Waterhouse-Friderichsen syndrome, Addison's disease
   (b) Pituitary hypofunction—Simmond's disease
   (c) Thyroid hypofunction—Hypothyroidism
5. Central nervous system
   (a) Trauma
   (b) Suprasellar cysts
   (c) Meningitis
6. Physiological imbalance
   (a) Newborn and premature infants
   (b) Post-operative interval

B. Hyperinsulinism, absolute
1. Alimentary
   (a) Physiologic (post-prandial)
   (b) "Dumping syndrome"
   (c) "Functional hypoglycemia"
2. Pathological lesions of the pancreas
   (a) Islet cell tumors of the pancreas
   (b) Hyperplasia of the islet cells of the pancreas
3. Idiopathic
4. Induced
   (a) Shock therapy

Relative hyperinsulinism is self-explanatory and will not be further exemplified.

Alimentary Hypoglycemia

Physiological (post-prandial) hypoglycemia is the commonest type of absolute hyperinsulinism. A normal response in a glucose tolerance test may be a slight hypoglycemia at 2 or 3 hours. This results from a high blood glucose level which stimulates increased output of insulin. An exaggerated insulin response occurs which must be adjusted before the blood glucose returns to its previous level. A continued high carbohydrate intake over a period of days leads to a flattening of the glucose tolerance curve, known as the Staub-Traugott phenomenon.

The dumping syndrome is an exaggeration of the normal glucose curve, occurring in patients following sub-total gastrectomies or gastroenterostomies, who have a large quantity of ingested glucose presented immediately to the intestinal mucosa for absorption. Very high blood sugar levels are therefore reached ½ to 1 hour post-prandially, leading to an outpouring of large quantities of insulin and clinically significant hypoglycemia at 2 or 3 hours.

Functional hypoglycemia represents another type of dysfunction of the normal glucose tolerance curve. It is presumably due either to increased sensitivity to normal amounts of insulin in response to a normal stimulus of hyperglycemia, or to increased sensitivity to normal amounts of adrenalin. The post-prandial rise in blood sugar levels is likely to be diminished in quantity and the rebound at 2 or 3 hours is exaggerated. This is the concept of Conn[1]; however there are conflicting views as to what constitutes a functional hypoglycemia. Rector and Jennings[2] and Grotts[3] have used the term to mean any type of idiopathic hypoglycemia. This would appear to be confusing. Conn's views are more acceptable at present.

Functional hypoglycemia is not progressive in severity. Attacks become more frequent under emotional or physical tension and characteristically occur 2 to 4 hours after a meal. In contradistinction to organic hyperinsulinism, attacks do not occur in the early morning before breakfast.

Pathological Lesions Of The Pancreas

In 1924, shortly after the discovery of insulin, Harris[4] postulated the existence of hyperinsulinism as a disease entity. He shortly thereafter described several cases with typical symptoms of hypoglycemia. These cases were considered to be due either to hyperplasia of the islet tissue, such as is known to occur in infants born of diabetic mothers[5, 6, 7, 8] or else to actual islet cell tumors. The first islet cell tumor was found by Wilder and his associates[9] in 1927. Finney and Finney[10] in 1928 performed the first operation on a patient with an islet cell tumor. The first large scale study was done by Whipple[11] who collected 75 cases of "hyperinsulinism" reported in the literature up to 1935; 21 of these patients were found to have a tumor at operation, and 10 others at post-mortem. Sixteen were explored but no tumor was present. A tumor was found in 31 patients without any known hypoglycemic symptoms. Whipple's own cases included 8 tumors removed from 6 patients. He stated that the adenomata were likely to be present in the tail and the body of the pancreas rather than in the head and were usually encapsulated. Of the 62 cases of tumor proven in Whipple's series only 4 were known to be malignant. According to the existing literature these tumors are quite rare in children. None of Whipple's 62 cases was under 18 years of age, with the exception of one originally reported by Wolf[12] in a child 10 years of age.

A review by Howard, Moss and Rhoades[13] in 1950, included 398 cases from the literature. Of these 161 were found at autopsy and 200 at operation for hyperinsulinism; 37 of the series were malignant clinically and morphologically.

In Howard's series, 14 patients were under 15 years of age, 5 of them under one year. Ten of these had benign adenomata, 2 had hyperplasia on

microscopic section; in 2 others a normal pancreas was found. None of the children had malignant tumors. The results in the children were somewhat less successful than in the adults. Four died postoperatively, 5 were apparently cured, and 2 others were cured of their hypoglycemia but were mentally retarded. The others showed no improvement.

In a survey by McQuarrie[14] of 40 patients with spontaneous hypoglycemia, admitted to the pediatric service of the University of Minnesota Hospitals during a 12 year period, only one case was found to have an islet cell tumor.

Idiopathic Hypoglycemia

Persistent hypoglycemia occurring in infants spontaneously and without any known cause has been well described by McQuarrie[14]. Because of the paucity of distinguishing stigmata the diagnosis may be long delayed or else an erroneous diagnosis of "idiopathic epilepsy" may be made when convulsions recur at frequent intervals unaccompanied by fever. This mistake is particularly liable to occur when blood sugar determinations are not made. Other clinical disorders, exhibiting hypoglycemia as a clinical manifestation, usually have additional, easily recognized features, such as hepatomegaly in glycogen-storage disease, cataracts and growth arrest in galactosemia, abnormal skin pigmentation and Addisonian crises in most cases of adrenal insufficiency, cretinoid appearance and behavior in severe hypothyroidism, and dwarfing in pituitary insufficiency. According to McQuarrie this type of spontaneous idiopathic hypoglycemia is an anomalous disturbance in carbohydrate metabolism and is not a fixed or permanent condition, but tends to undergo spontaneous adjustment as the child gets older.

In the 40 cases of hypoglycemia studied by McQuarrie 25 or 62.5% fit into this category of spontaneous idiopathic hypoglycemia.

The mechanism of these types of spontaneous hypoglycemia is reasonably clear and it is felt to be due to deficiency in one or more of the hyperglycemic factors without compensatory decrease in insulin secretion.

Recent experimental studies have suggested that absence of glucagon, the hyperglycemic-glycogenolytic factor thought to be produced by the alpha cells of the pancreas, may result in spontaneous hypoglycemia[14].

In McQuarrie's 25 cases of idiopathic spontaneous hypoglycemia[14, 15] the age of onset varied between the first day of life (2 cases) and 5 years. In 21 of the 25 the age of onset was under 2 years. Alpha cells in the islets of Langerhans on biopsy of the pancreas were absent in 2 familial cases[16].

The importance of early diagnosis in these cases should be stressed since mental deterioration and permanent cerebral damage may result from repeated hypoglycemic episodes.[17, 18, 19] McQuarrie has studied this entity extensively and has found by using the standard functional tests currently

available that there are no deficiences in the functions of the liver, pituitary, thyroid or adrenal glands. Urinary assays for 17-ketosteroids and 11-oxysteroids, likewise, show no evidence of abnormality. McQuarrie has been impressed with the strong familial or hereditary aspect.

Induced Hypoglycemia

This type of hypoglycemia is produced therapeutically in patients given insulin shock therapy for psychoses. This type of treatment is, however, not without danger since extensive destruction of the cortical neurones has been found in these patients following insulin shock therapy. Lesions have been found particularly in the third and fourth layers of the cerebral cortex as well as the lenticular nuclei.

DIAGNOSIS

The symptoms, as previously discussed, especially in the presence of unconsciousness or convulsions, should prompt an estimation of the fasting blood sugar. However, if only mild nervous symptoms are manifest, the diagnosis is more apt to remain undetected. If the symptoms disappear as the blood sugar concentration is increased, a diagnosis of pathologic hypoglycemia can be concluded. The determination of the etiology of hypoglycemia rests on laboratory investigations of carbohydrate metabolism.

LABORATORY INVESTIGATIONS

Oral Glucose Tolerance Test

Mayer and Womack[23] studied the glucose tolerance curve in large numbers of normal subjects using the method of Folin and Wu for blood sugar determination. They felt that the fasting blood sugar should always be below 120 and the two-hour level usually below 125 in the oral test or 114 mg./100 ml. in the intravenous test. Levels above 140 and 127 mg./100 ml., respectively, at two hours were felt to be indicative of diabetes or at least of a diabetic-type curve. According to Fraser, Albright, and Smith[24] the hyperglycemia unresponsiveness which constitutes a positive oral or intravenous glucose tolerance test can be due either to insulin lack (diabetes mellitus) or to insulin resistance. Figure 2 illustrates the typical responses to the glucose tolerance test.

Intravenous Glucose Tolerance Test

This test eliminates the need to consider the factor of glucose absorption from the gastro-intestinal tract. If hypoglycemia is produced within four to six hours, a deficiency of adrenocortical SFN hormone or the HG factor (hyperglycemic-glycogenolytic factor) of the alpha cells of the pancreas is

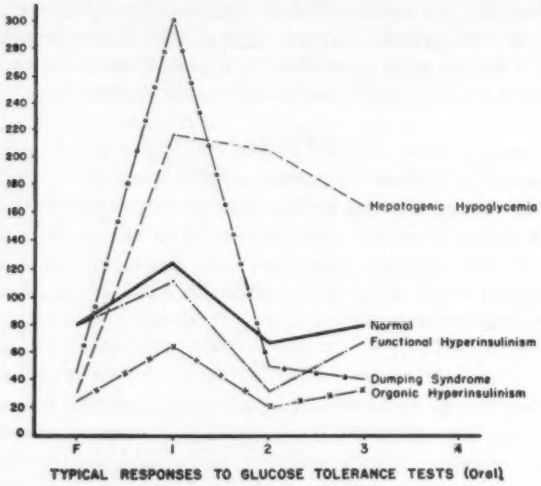


FIG. 2

assumed to be present, since it is these mechanisms which are brought into play to counteract insulin secretion.

By the use of ACTH before the administration of the intravenous glucose, a deficiency in anterior pituitary function is ascertained if the hypoglycemia is so abolished. Likewise, if cortisone abolishes this effect, adrenocortical hypofunction can be postulated.

Insulin Tolerance Test

In this test one is looking for both insulin resistance and hypoglycemia unresponsiveness. The test is not without its dangers and should be done under constant observation with intravenous glucose readily available if necessary. Since the test adds very little information and poses potential dangers to the patient it should not be undertaken indiscriminately.

Exton-Rose Two Dose Glucose Tolerance Test

This test was originally proposed by Exton and Rose[25]. The theory of the test is that the first dose of glucose produces maximal outpouring of insulin in response to hyperglycemia, and that the second dose then subjects the blood sugar mechanism to extreme stress. The test has been used chiefly to study diabetics.

Adrenalin Tolerance Test

The ability of the liver to convert glycogen to glucose is measured by this test. This capacity is deficient in von Gierke's disease as well as in liver disease in general.

Insulin Assays

Clearly an etiologic classification based on absolute versus relative hyperinsulinism would be augmented by a direct determination of the quantity of insulin.

Mirsky et al[26] developed a technique for the measurement of insulin in the urine. However, this assay is extremely time consuming and intricate, and involves many technical difficulties which prevent its being applicable for general use. Determination of plasma insulin is also possible but rarely done.

Electroencephalography

Repeated electroencephalographic tests are useful in determining any progressive cerebral deterioration. It is recommended that blood sugar measurements be done at the time of each test inasmuch as the effect of hypoglycemia on suppressing the alpha cortical rhythm is well known[27, 28, 29]. If a delta rhythm is not actually present the amount of hyperventilation required to produce one may be diminished in the presence of hypoglycemia. In patients with infrequent attacks of hypoglycemia, electroencephalographic changes are usually not present between attacks.

TREATMENT

The immediate symptoms of hypoglycemia can be relieved by the intravenous administration of glucose. As suggested by Conn[30] the management of functional hypoglycemia is dietary, consisting of a high protein and a low carbohydrate intake. In hepatic hypoglycemia the diet should be high in carbohydrate and protein. Islet cell adenomata are uncommon in children, but, if suspected, laparotomy should be performed. Recent advances in the therapy of idiopathic spontaneous hypoglycemia of infancy have been made by McQuarrie[14]. The functional antagonism between the anterior lobe of the pituitary gland and the islets of Langerhans[20, 21, 22] led this author to a therapeutic trial of adrenocorticotropic hormone for its pituitary diabetogenic effect in cases of spontaneous idiopathic hypoglycemia. All of his reported cases have responded favorably to treatment with adrenocorticotropic hormone. He suggests that therapy be instituted as follows:

"Adrenocorticotropic hormone intramuscularly 4 mg. per kilogram of body weight (or 100 mg. per square meter of body surface) per day, given in four equal doses at six hour intervals for 4 days. The following week, one-fourth of this dose (1 unit per kilogram of body weight per 12 hours) is given night and morning in the form of H. P. Acthargel (The Armour Laboratories).

"If the fasting blood sugar remains normal with this dosage schedule the morning dose is omitted during the succeeding few weeks.

"The criteria for guidance during extended periods of treatment are maintenance of a symptom-free state and fasting blood sugar levels above 40 mg. per 100 ml. The dosage of corticotropin must be adjusted for the individual patient."

In a patient with protracted hypoglycemia who is unresponsive to all other types of therapy, one may resort to partial pancreatectomy. However this has had little, if any, palliative effect.

CONCLUSION

In considering a new patient with hypoglycemia, effort should be made to rule out the known types of relative hyperinsulinism. The most important of these is the hepatic group, which should be readily recognized by liver function tests, deficient blood glucose response to adrenalin, and the hepatic type of glucose tolerance curve which rises at four hours but falls to a hypoglycemic level at 6 hours. These patients are likely to have their symptoms in the morning or following fasting. Pituitary and adrenal integrity can be estimated by the use of ACTH and cortisone in glucose tolerance tests. Most of the other types of extra-pancreatic relative hyperinsulinism can be readily ruled out on the basis of history and physical examination.

It is most important to recognize the islet cell adenoma in the absolute hyperinsulinism group. Islet cell adenomata are uncommon in children. No strong argument can be made for surgical intervention in children on the grounds of possible malignancy since it is not readily apparent that any case of a malignant islet cell tumor has been reported in a child.

The "functional" type of hypoglycemia should be relatively easy to identify by the timing of the symptoms and the glucose tolerance curve. This group should be relatively susceptible to dietary management.

It is most important to recognize spontaneous idiopathic hypoglycemia of infancy as severe hypoglycemic episodes may lead to irreparable brain damage. In these cases, except for the low fasting blood sugar, the functional tests show no abnormality. The response to therapy with ACTH in this condition, as shown by McQuarrie[14] is dramatic.

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Addition

A recent publication by Warren (Warren, K W., Non-functioning Islet Cell Carcinoma in an 11 year old child treated by pancreatoduodenectomy. Lahey Clin. Bull. **9:** 155, 1955) describes a case of islet cell carcinoma in an 11 year old child. This tumor was non-functioning and produced no symptoms of hypoglycemia.

CLINICAL PATHOLOGICAL CONFERENCE

Discussed by Charles R. Webb, M.D.
Directed by Grace H. Guin, M.D.
Assisted by Enid F. Gilbert, M.D.

PROTOCOL

This white male infant was the product of a normal full term gestation and normal delivery at the U. S. Naval Hospital, Bethesda, Maryland. Birth weight was 5 lbs. 13 oz. Soon after delivery the baby became rigid and cyanotic. Spinal and sub-dural taps were performed and were negative. Following this the patient gained very slowly and ate very little. There was a profuse chemical conjunctivitis and an infected circumcision. Following discharge he did poorly and at the age of 17 days he was seen by a pediatrician because of slowness to gain weight, intermittent cyanosis, and diarrhea. The cyanosis was intensified by crying. There were no convulsions. At this time the patient was admitted to Children's Hospital for the first time.

On physical examination he was fairly well developed but dehydrated. The weight was 6 lbs. 6 oz.: temperature 100°. There were a few maculopapular lesions on the buttocks. The pharynx was slightly injected. No cyanosis was noted. The lungs were clear to percussion and auscultation. The heart sounds were regular and no murmurs were heard. No abdominal masses were palpable. Liver, spleen, and kidneys were not felt. Neurological examination revealed no abnormal findings. Examination of the blood showed a hemoglobin of 20 gms. per 100 ml., 5.7 million red cells, 10,600 white cells, 24 per cent segmented, 13 per cent bands, 62 per cent lymphocytes, and 1 per cent monocytes. On x-ray examination of the chest, there was a shadow about the right cardiac border which was interpreted as an enlarged thymus. X-ray therapy was given and the patient was discharged 2 days after admission on a satisfactory feeding schedule. The patient was readmitted approximately 2 weeks later at the age of 5 weeks. At this time, the infant appeared in acute respiratory distress. He had apparently done well until 4 hours prior to admission when he became acutely cyanotic and dyspneic.

Physical examination at this time showed acute respiratory distress with generalized cyanosis which was particularly marked on the extremities. There were a few rhonchi over the left side of the thorax, which presented a crepitant feeling to touch during artificial respiration. The temperature was 97.0°. The baby was placed in an oxygen tent immediately, but the respirations gradually became gasping and the pulse feeble. Caffeine sodium benzoate, adrenalin, and coramine failed to revive the infant. Death occurred 3½ hours after admission.

DISCUSSION

Charles R. Webb, M.D.

This case presents an interesting problem in that the differential diagnosis could properly envelop all the causes of cyanosis and convulsions in the newborn. Let us consider first the possibilities that existed at the time of birth. These should include: (1) intracranial bleeding of all types, (2) septicemia, (3) cardiovascular lesions, (4) lesions of the respiratory system, (5) blood dyscrasias.

Although no mention was made of traumatic delivery or of a breech delivery, the possibility that the cyanosis and rigidity were secondary to a subdural hematoma or a tear of one of the tentorial vessels cannot be ruled out from the information furnished despite the negative spinal and subdural taps. No mention is made of neurological abnormalities but an absent Moro reflex and a positive Foote's sign, which is the adder-like protusion of the tongue, might have been helpful had they been noted. As you know, a shrill cry, paralysis of various muscles, and retinal changes would also have pointed towards intracranial hemorrhage. The rigidity and cyanosis, the infected circumcision, and the chemical conjunctivitis may suggest the possibility of a generalized septicemia which may have occurred from the infected circumcision. Cardiovascular lesions of the type which produced cyanosis usually do not follow the course that has been indicated in this protocol. Among lesions of the chest that we might properly consider are first of all, aspiration of amniotic fluid, hyaline membrane disease, pneumonia, and the possibility that the baby has had a diaphragmatic hernia with eventration of the gut into the chest. Singular or multilocular cysts of the lung also should be considered. Thymic enlargement and tumors and other mediastinal masses do not usually produce such a dramatic symptomatology. Congenital atelectasis, pneumothorax, and congenital laryngeal stridor or laryngeal web usually do not present a picture of intermittent cyanosis without respiratory signs. Again, under blood dyscrasias, kernicterus could produce such a picture but usually not at birth. There is no indication that the child had an Rh or an ABO incompatibility. No mention is made of these factors nor is any note made of jaundice. Again it might be noted that kernicterus is rarely seen as an isolated case of rigidity and cyanosis without some indication that the child had become jaundiced prior to this.

Let us consider the findings at the time of admission, when the child was 17 days old: intermittent cyanosis, failure to gain weight, and diarrhea. There were no convulsive episodes at this time. The intermittent cyanosis, it may be noted, was increased by crying. Again we have the possibility that this child had a subdural hematoma or other neurological findings. The blood count taken at this time was well within normal limits, and the

x-ray of the chest showed nothing except a shadow at the right cardiac border which was interpreted as an enlarged thymus. The possibility that this was a mass of another sort exists; the possibility of cyanotic heart disease cannot be ruled out. The cyanotic lesions include: tetralogy of Fallot; Eisenmenger's syndrome, pulmonary stenosis, tricuspid stenosis, transposition of the great vessels, and triloculate heart. Aortic arches in abnormal positions should be considered, and I think a barium swallow might have been of value at this time. Rhabdomyoma of the heart may also occur. The general way the child progressed would certainly militate against endocardial fibroelastosis.

Two weeks later this infant came to the hospital with a sudden onset of acute respiratory distress and generalized cyanosis. He had rhonchi in the chest and crepitation to the touch. This would certainly lead one to believe that the exodus of this patient was of a respiratory nature. However, on the basis of the information that we have we cannot rule out the possibility of cyanotic heart disease. Dr. Lattman has just been kind enough to check this x-ray film, which is interpreted as showing a mass at the right border of the heart and his suggestion, that there is possibly a little haziness of the

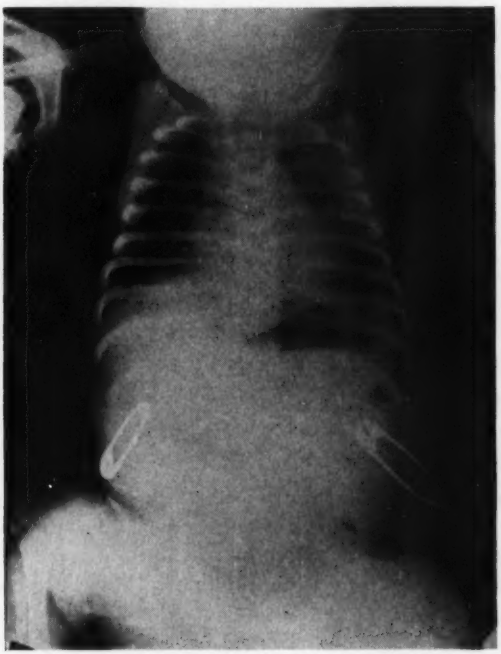

FIG. 1.

FIG. 2.

left diaphragmatic leaf, may give us the indication that the child could have had a sudden herniation of viscera into the left chest. However, in view of the fact that the x-ray of the previous episode was considered negative this diagnosis could not be made.

In summing up I would like to attribute this death to respiratory causes and feel that probably an *acute pneumonic process* or a sudden *rupture of a congenital lung cyst* was the cause. I will hedge a little on my diagnosis and say that I would not be too surprised if the child did have a congenital heart lesion.

PATHOLOGY

Enid F. Gilbert, M.D.

At autopsy the body was that of a well developed white male infant. There was cyanosis of the fingers, toes and mucous membranes. The skin was normal and the subcutaneous tissues scanty. On opening the thorax 70 ml. of turbid fluid was found in the left pleural cavity. Half of the entire length of the small intestine had herniated through the diaphragm and was found in the left pleural cavity. The left lung was displaced upwards and compressed. There was a shift of the mediastinum to the right. The pleural

cavity and the right lung appeared normal. The dome of the diaphragm was situated at the level of the fourth intercostal space on the right side and the fourth rib on the left side. A valve-like opening 2.5 cm. in diameter was found in the left dome of the diaphragm 1.5 cm. to the left of the midline. Through this opening the loops of small intestine had herniated into the left pleural cavity. The margin of the opening was smooth with no evidence of fibrosis or inflammation.

On opening the abdomen about 10 ml. of turbid fluid was found in the peritoneal cavity. The intestinal loops were markedly distended. The stomach was displaced to the left and its usual position was occupied by a loop of dusky red intestine.

The heart was displaced to the right and there was dilatation of the right auricle. The right lung weighed 48 grams and the left 21 grams compared with the normal of 31 and 27 grams respectively for an infant of this size. The left lung was collapsed and grayish red. The right lung was soft, pinkish gray and crepitant. The liver, spleen, pancreas, adrenals and kidneys were grossly unremarkable. The stomach was markedly distended with air and contained 50 ml. of milky material. The small intestine was dark red. The mucosa of the duodenum and front part of the jejunum was bright red. The mucosa of the distal portion of the small intestine was dusky red. The lymph follicles were prominent. The mesenteric vessels were congested and prominent. No abnormalities of the large intestines were seen. The brain showed engorgement of the meningeal vessels.

On microscopic examination sections from the left lung showed diffuse atelectasis. In the right lung there were focal areas of atelectasis. There was slight interstitial edema of the myocardium. The liver showed polymorphonuclear cells in the sinusoids; no other changes were seen. The splenic sinusoids were congested. The stomach was unremarkable. There was congestion and hemorrhage into the submucosa with some loss of the surface epithelium throughout the small intestine. The lymph follicles were hyperplastic. Numerous small cysts were found in the cortices of the kidneys, the linings of these cysts being a thin layer of fibrous tissue. The remainder of the kidney parenchyma appeared normal. The thyroid, pancreas, bladder and generative organs were not remarkable. The brain tissue was congested.

Pathological Diagnosis

1. Congenital hernia of the diaphragm.
2. Herniation of the intestines into the thoracic cavity.
3. Secondary atelectasis of the lungs due to herniation of the intestines.
4. Multiple cysts of the renal cortices.
5. Congestion and hemorrhage of the small intestines.
6. Pleural and peritoneal effusion.

PATHOLOGY DISCUSSION

Grace H. Guin, M.D.

Congenital diaphragmatic hernia is one of the commonest forms of defective development occurring as an isolated defect in an otherwise normal child. The defect in the diaphragm is more likely to be large than small. The majority of hernias is located on the left side in a postero-lateral position, in the foramen of Bochdalek. This patient furnishes an example of this type.

In this hospital autopsies have been performed on 5 children who died with congenital diaphragmatic hernia since 1947. The defect in 4 patients was located in the left side. It was the only congenital abnormality in all patients except 1 child who had congenital heart disease and other deformities. The youngest was 1 day of age and the oldest was 2 years at the time of diagnosis. All of the children displayed symptoms referable to the respiratory tract. Invariably these include dyspnea and cyanosis. In 2 of the patients surgical repair was undertaken for the second time because of recurrence. One of these died of intestinal obstruction, another because of sudden change in hemodynamics incurred when the abdominal organs suddenly entered the chest. The youngest patient expired during repair of the hernia. Another expired because of congenital heart disease. Death of the fifth child was due to shock and pneumonitis following rupture of the stomach after it had entered the pleural cavity.

NEWS AND NOTES

Dr. Richard Todd of the Attending Staff of Children's Hospital is President of the local medical society orchestra this year; Richard Dirksen conducts. The first concert will be held October 11th at the 25th annual Scientific Assembly of the Medical Society of the District of Columbia, with 4 or 5 more concerts to follow this year. The orchestra is open to physicians, dentists, veterinarians, pharmacists and their families.

Dr. Harold Stevens, who serves as Chief of Neurology at Children's Hospital has been appointed to the position of Professor of Neurology at the George Washington University School of Medicine to replace Dr. Walter Freeman who resigned.

Anthony P. DeSpirito, M.D., announces the opening of his office for the practice of Pediatrics at 611 Sunset Avenue, Asbury Park, N. J.

Bennett Olshaker, M.D., announces the limitation of his practice to Pediatric Psychiatry at 4435 35th Street, N.W., Washington 8, D. C.

Robert L. Bregman, M.D., announces the opening of his office at Suite 1, 3515 Mount Vernon Avenue, Alexandria, Virginia with practice limited to Pediatrics.

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